Questions to the Committee

Certican (everolimus)
NDA 21-628
Novartis
Pharmaceuticals
November 16, 2005

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardiovascular and Renal Drugs Advisory Committee

---

1. Novartis has presented the results and extensively discussed the use of a 'fixed-dose' everolimus regimen with "full-dose" cyclosporine in study B253. Both FDA and Novartis agree that this exact fixed-dose regimen should not be used for the prophylaxis of organ rejection in cardiac transplantation. Do committee members agree with this conclusion?

2. Novartis has proposed an alternative 'TDM-based' regimen for the use of everolimus in combination with cyclosporine. The proposed regimen has not been prospectively tested in a cardiac transplantation study. In the absence of a prospective study of this regimen, do committee members believe there is sufficient information available to conclude that the regimen as proposed by Novartis has been demonstrated to be safe and effective for use in heart transplantation?

    a. In your discussion, please be specific regarding what information supports the proposed TDM-based regimen.

    b. Please discuss in your answer whether you believe that everolimus has been shown safe and effective for all cardiac transplant recipients.

    c. Alternatively, please discuss whether you believe there are certain subgroups where use should be specifically indicated or specifically restricted.

3. If your answer to question #2 is yes, that the proposed TDM-regimen is safe and effective, please comment on what additional information should be obtained regarding everolimus post-approval. Additionally, do you have any recommendations regarding labeling (package insert).

4. If your answer to question #2 is no, please comment what additional information would be necessary for approval. For example, please comment whether the currently-ongoing European study and/or the planned US cardiac transplantation study would be adequate to demonstrate safety and efficacy. Also comment whether additional data or studies would be necessary.